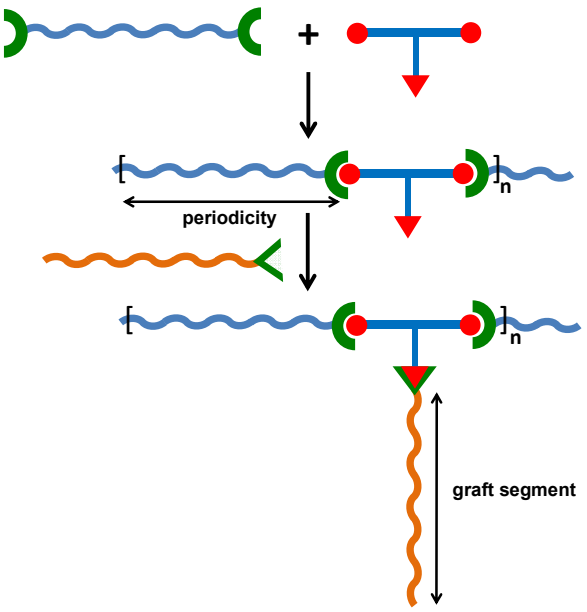
Synopsis

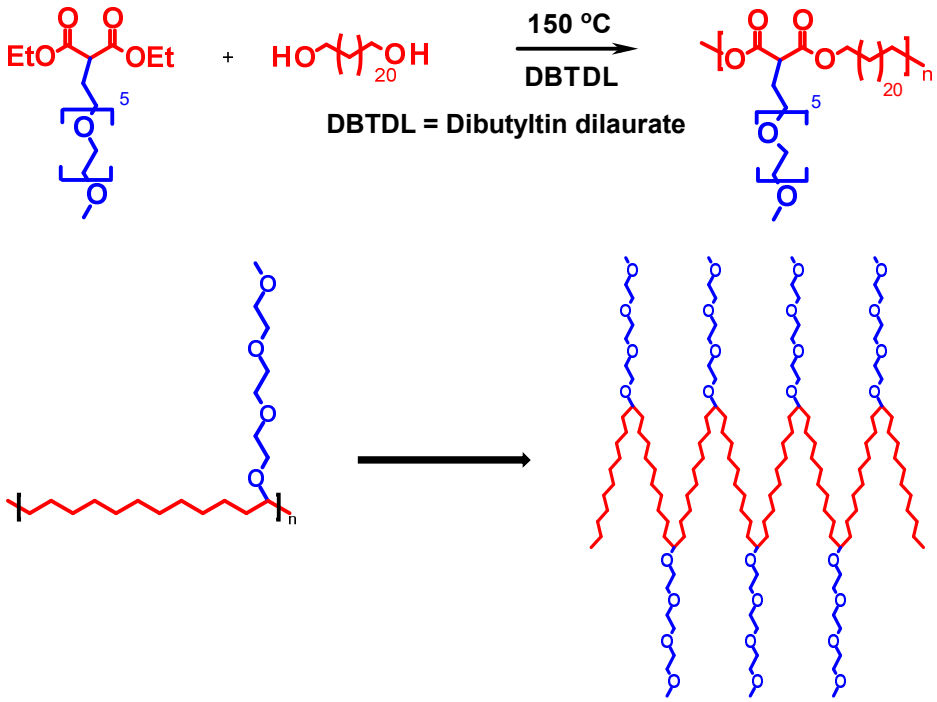
Block copolymers can self-assemble into a variety of periodic nanostructures and therefore, are promising candidates for a diverse range of applications. While self-assembly of block copolymers has been widely studied and exploited, graft copolymers have remained far less explored in this context. One of the primary reasons for this is that the most commonly used methods to prepare graft copolymers leads to polymers that do not have precisely defined structures; specifically, controlling the precise location of the grafted segments is a synthetically difficult challenge.

In typical chain polymerization processes, statistically random incorporation of monomers takes place and consequently, the periodicity of the grafted segment along the backbone is very difficult to control precisely; therefore, such methods cannot be utilized to prepare periodically grafted copolymers. Some recent efforts towards the preparation of sequence regulated copolymers using controlled radical polymerization in conjunction with periodic dosing of a comonomer could provide an alternative to better regulate the periodicity, although this will also not be perfectly periodic. The only approach to control the periodicity perfectly is to utilize condensation polymerization approaches, wherein one of the monomers serve as a spacer whereas the other provides the opportunity to install the graft segment, as depicted in Scheme 1. One of the earliest examples of the utilization of a condensation approach to locate desired units at periodic intervals was reported by Wagener and coworkers using Acylic Diene Metathesis (ADMET) process.[1]



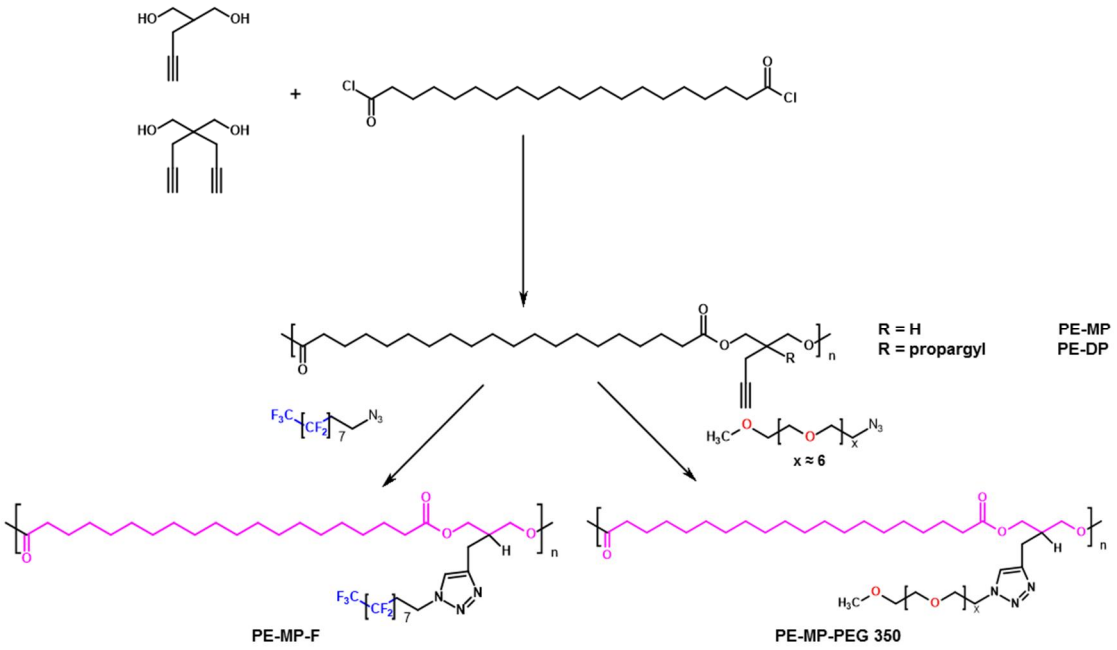
Scheme 1. *Synthetic scheme for the preparation of periodically grafted copolymers using condensation polymerization.*

From our lab, Roy et al. developed periodically grafted amphiphilic copolymers (PGAC), based on a readily available starting material, diethyl malonate;[2] melt trans-esterification between diethyl malonate, containing a pendant hexaethylene glycol monomethyl ether (HEG) segment and 1,22-docosane diol resulted in PGAC wherein the hydrophilic oligoethylene glycol units were placed on every 27th atom along the backbone (Scheme 2). Such PGAC underwent self-segregation and adopted a folded zigzag conformation, which was driven by the intrinsic immiscibility of the alkylene and HEG segments and was reinforced by the strong tendency for long chain alkylene segments to crystallize in a paraffinic lattice. However, one of the drawbacks of the above approach was that the hydrophilic pendant unit was installed at the monomer stage and consequently, the synthetic approach does not allow easy variation of the hydrophilic grafted segment; this limits the flexibility and any structural variation of the pendant segment would be synthetically tedious.



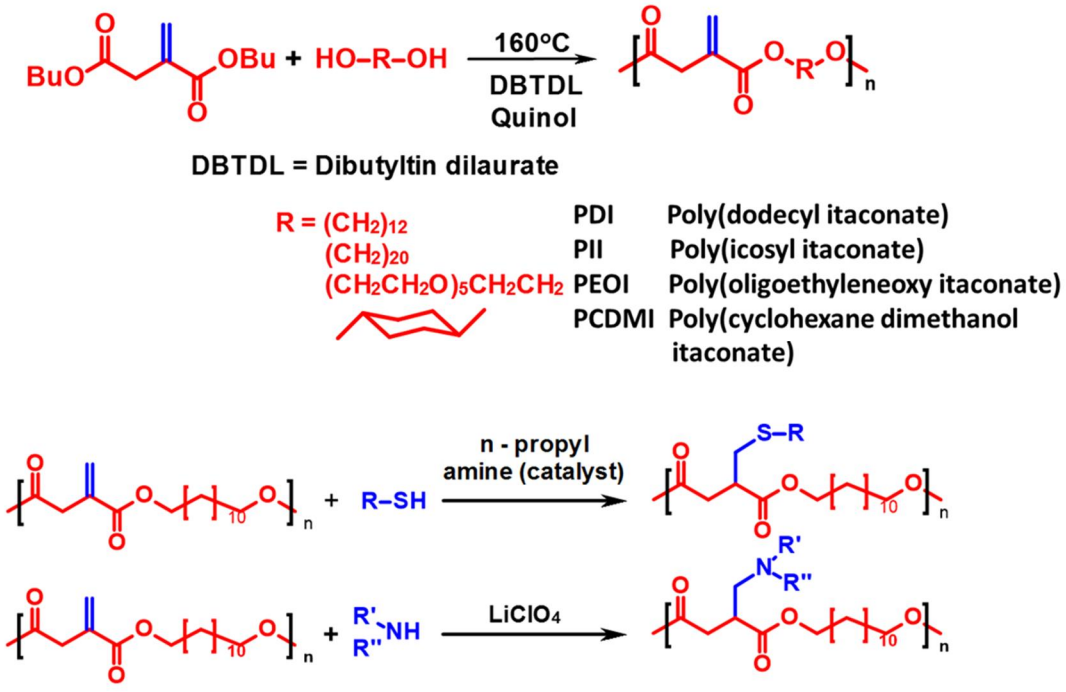
Scheme 2. *Synthesis of PGAC, based on diethyl malonate, and immiscibility-driven folding of such PGACs.*

Mandal et al. developed a more general strategy for the synthesis of such periodically grafted systems; they prepared periodically clickable polyesters carrying propargyl groups at regular intervals, by the solution polycondensation of 2-propargyl-1,3-propanediol or 2,2-dipropargyl-1,3-propanediol and the acid chloride of 1,20-eicosanedioic acid. Such periodically clickable polyesters were shown to react quantitatively with a fluoroalkyl azide[3] and PEG 350 azide[4], thus allowing them to place different kinds of functionalities precisely along the backbone, as shown in Scheme 3. The immiscibility of the alkylene and fluoroalkyl/PEG segments caused the polymer chains to fold in a zigzag fashion, thereby facilitating the segregation of these segments, as observed earlier in the study by Roy et al.[2] The objective of this study was to place various desired functionalities along the polymer backbone and examine their effect on the self-assembly behaviour and morphology of such periodically clicked systems.



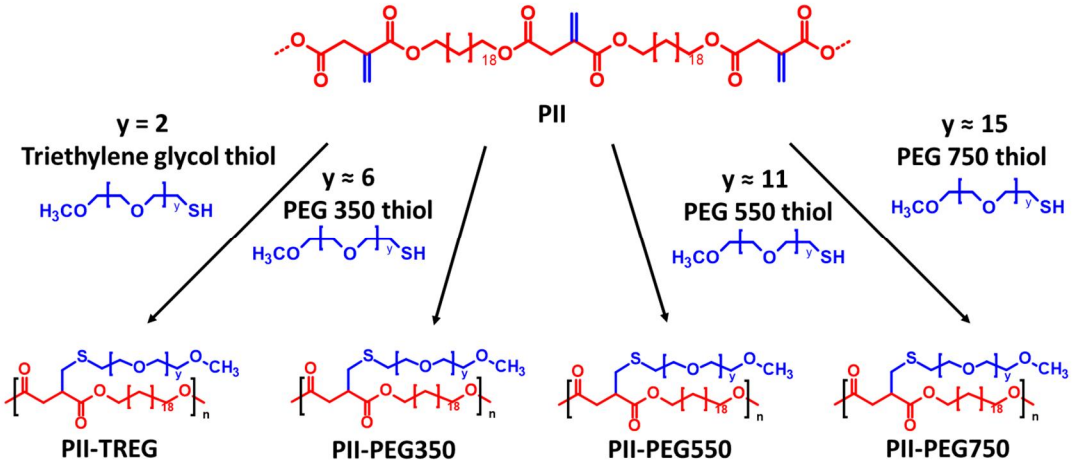
Scheme 3. *Synthetic scheme for the generation of periodically clickable polyesters and their subsequent functionalization via Cu-catalysed click chemistry.*

In Chapter 2, we describe an alternative general strategy for the scalable synthesis of periodically graftable polyesters and their subsequent functionalization to generate a wide variety of periodically grafted systems. The importance of our approach lies in our choice of the monomer, which is based on itaconic acid, an inexpensive and bio-sourced molecule. We demonstrated that dibutyl itaconate can be melt-condensed with aliphatic diols to generate unsaturated polyesters (Scheme 4); importantly, we showed that the double bonds in the itaconate moiety remain unaffected during the melt polymerization. A particularly useful attribute of these polyesters is that the exo-chain double bonds are conjugated to the ester carbonyl and therefore, can serve as excellent Michael acceptors. A variety of organic thiols, such as alkane thiols, MPEG thiol, thioglycerol, derivatized cysteine etc., were shown to quantitatively Michael-add to the exo-chain double bonds and generate interesting functionalized polyesters; similarly, organic amines, such as N-methylbenzylamine, diallyl amine and proline also underwent Michael addition across the double bond (Scheme 4). Thus, such poly(alkylene itaconate)s could be utilized to place diverse functionalities at regular intervals along the polymer backbone.



Scheme 4. *Preparation of periodically graftable polyesters, based on itaconic acid, and their subsequent modification by Michael addition.*

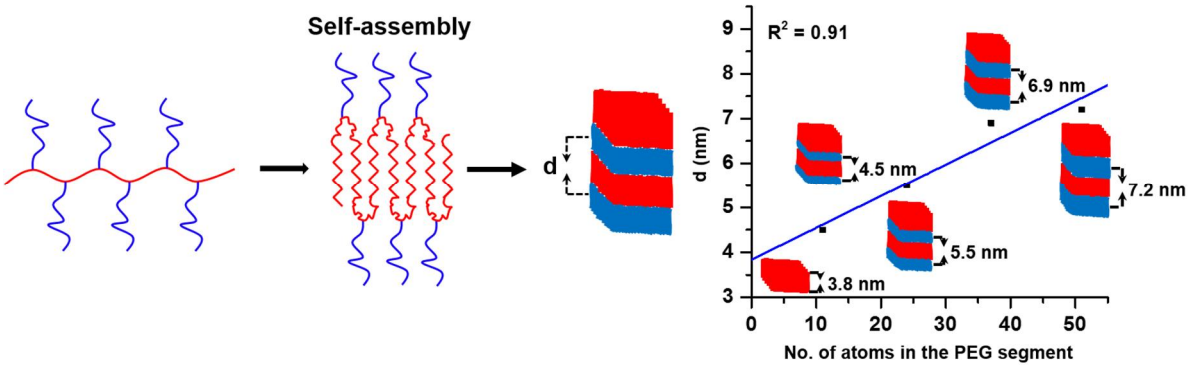
In Chapter 3, we examined a series of periodically grafted polyesters carrying long crystallizable alkylene (C-20) segments along the backbone and pendant polyethylene glycol monomethyl ether (MPEG) segments grafted at periodic intervals. Such periodically grafted amphiphilic copolymers (PGAC) having MPEG graft segments of varying lengths were prepared by utilizing the activated exo-chain double bonds in poly(icosyl itaconate) (PII) that carries a 20-carbon alkylene segment; MPEG thiols of varying lengths (TREG, 350, 550 and 750) were quantitatively grafted under standard Michael addition conditions to yield the required graft copolymers, as shown in Scheme 5.



Scheme 5. *Synthesis of a series of periodically grafted amphiphilic copolymers (PGAC) utilizing post-polymerization modification via Michael addition with MPEG thiols of varying lengths.*

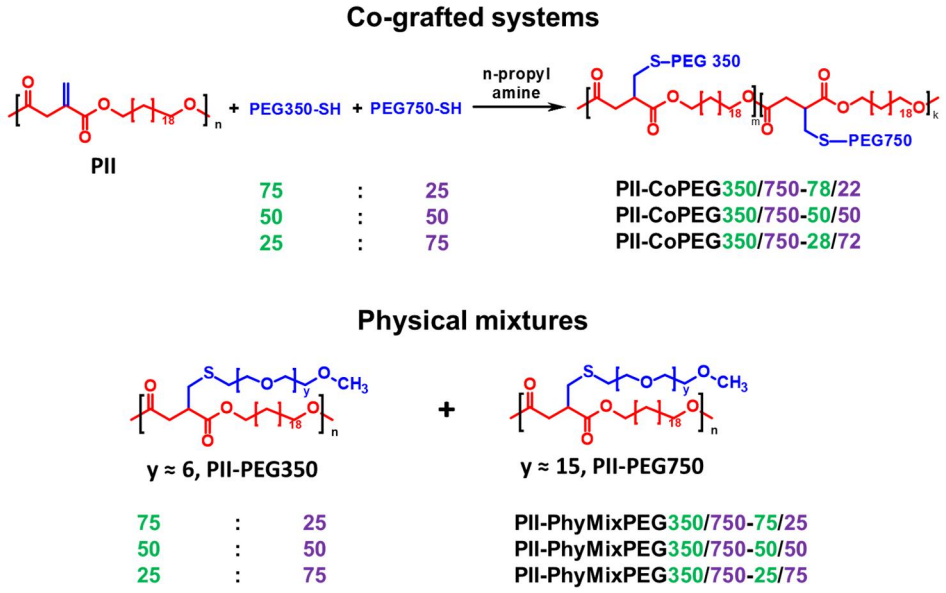
The immiscibility of the backbone alkylene and pendant MPEG segments, and the strong propensity of the alkylene segments to crystallize in a paraffinic lattice, drive these systems to fold in a zigzag fashion and subsequently organize into a lamellar morphology, as shown in Scheme 6. Interestingly, all the graft copolymers exhibited a clear and invariant melting transition at ~44°C that suggested the crystallization of the backbone C-20 segment; the MPEG segments were, however, amorphous except in the case of polymers carrying MPEG 550/MPEG-750 segments, wherein a second melting transition corresponding to the independent crystallization of the PEG segment was also seen. SAXS studies indicated that all of the samples exhibited lamellar morphologies wherein more importantly, the inter-lamellar spacing was seen to increase linearly with the MPEG length (Scheme 6). This study provides a new design for controlling the dimensions of the microphase-separated nanostructures at

significantly smaller length scales (sub-10 nm) than is typically possible using block copolymers.



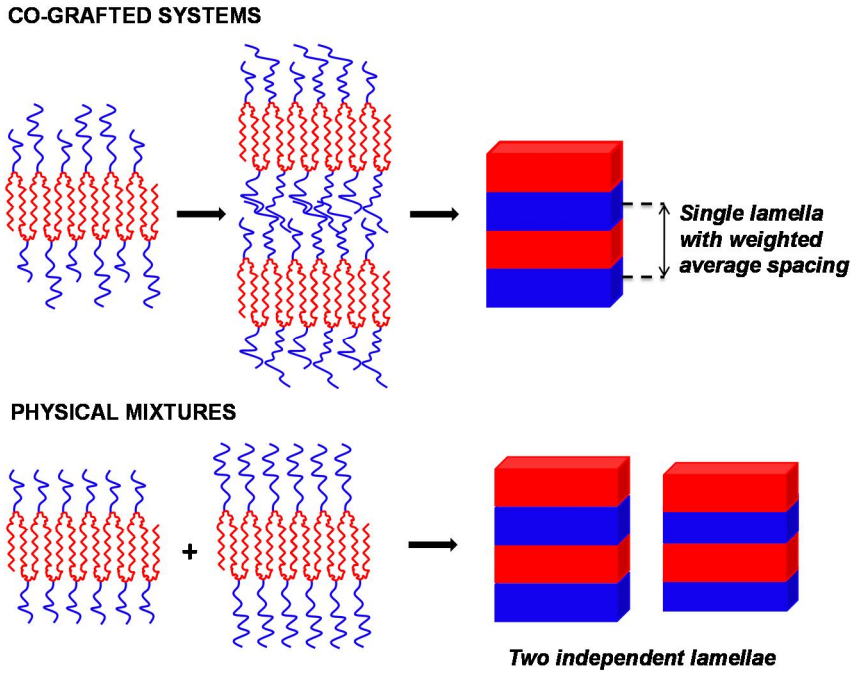
Scheme 6. *Schematic representation of formation of lamellar morphology in PGACs and control of interlamellar spacing in such systems.*

In order to understand the influence of having a mixture of MPEG lengths on the self-assembled morphology, in Chapter 4 we prepared a series of PGACs by co-grafting the parent poly(icosyl itaconate) with a mixture of two different MPEG thiols, namely MPEG-350 and MPEG-750; the mole-ratios of these two PEGs were varied to generate co-grafted PGACs, carrying different amounts of the two MPEG segments randomly distributed along the chain (Scheme 7). Parallely, we also examined the behaviour of physical mixtures of two different PGACs, one bearing MPEG-350 and the other MPEG-750 grafts; keeping the total MPEG content constant, we sought to examine the differences in the behaviour of randomly co-grafted polymers and physical mixtures.



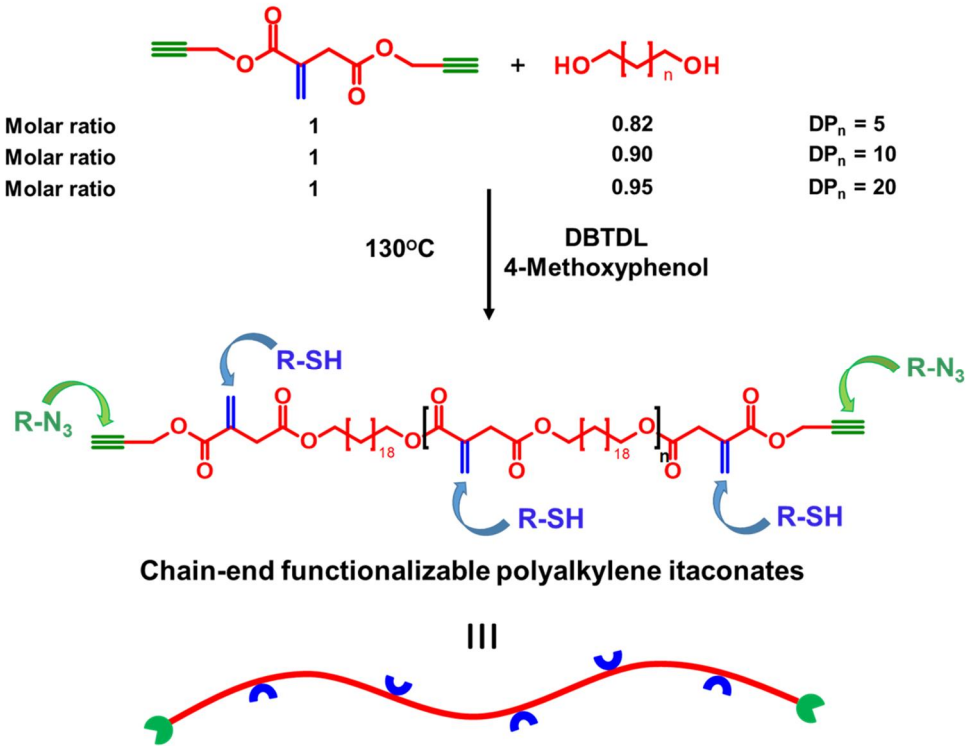
Scheme 7. *Preparation of co-grafted PGACs and physical mixtures of two different PGACs.*

The co-grafted PGACs also exhibited a lamellar morphology; interestingly, the inter-lamellar spacing increased linearly with the total volume of PEG domain. This suggested that despite the presence of MPEG segments of two different lengths in the co-grafted samples, there occurred a reorganization of the PEG chains within the amorphous domain ensuring that the condition of incompressibility is not violated, thereby giving rise to a weighted average interlamellar spacing, as shown in Scheme 8. In contrast, the SAXS patterns of the physical mixtures revealed the presence of two distinct lamellar domains in the sample; this indicated that the two homo-grafted samples do not mix and form separate lamellar domains. The self-segregation induced folding and subsequent crystallization of the central alkylene segments clearly appeared to dominate the final morphology.



Scheme 8. *Schematic depiction of the possible scenarios that could arise when MPEG segments of two different lengths, namely MPEG350 and MPEG750, are present in the PGACs; top panel depicts the co-grafted PGACs, whereas the bottom panel shows the case of mixtures of PGACs with two different MPEG lengths.*

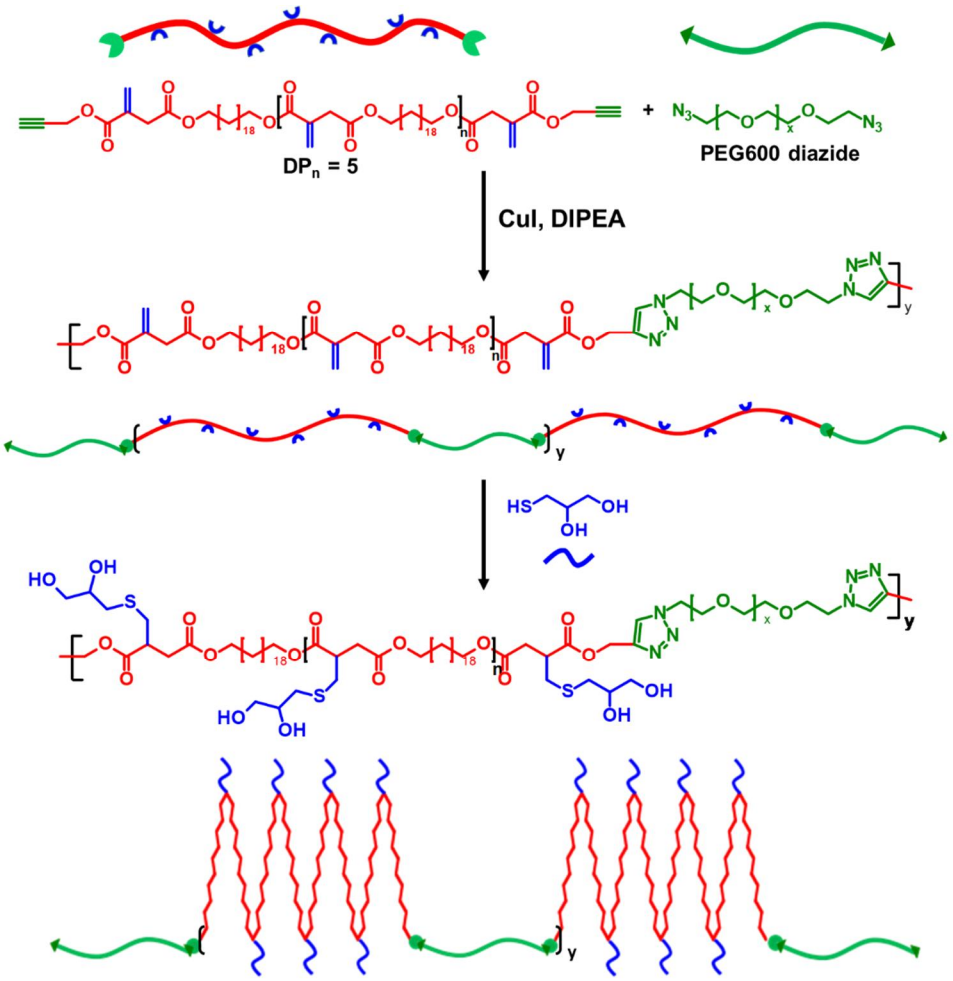
In Chapter 5, we have dealt with the design and synthesis of chain-end functionalizable polyalkylene itaconates. Changing the monomer from dibutyl itaconate to dipropargyl itaconate and using it in controlled excess allowed us to generate chain-end functionalizable polymers containing propargyl groups at the chain ends, in addition to the exo-chain double bonds along the backbone, thereby providing the opportunity for orthogonal functionalization. In order to obtain three different telechelic polymers with target DPs (degree of polymerization) of 5, 10 and 20 respectively, 3 different mole ratios of the two monomers (dipropargyl itaconate and 1,20-eicosanediol) were used (Scheme 9).



Scheme 9. *Synthetic scheme for the generation of chain-end functionalizable polyalkylene itaconates.*

Orthogonal functionalization of the resultant polymers was carried out using thiol-Michael addition and Cu(I)-catalysed alkyne-azide cycloaddition (AAC), without interference between the functional handles present along the polymer backbone and the chain-end, respectively. Michael addition with triethylene glycol thiol and subsequent Cu-catalysed click reaction with MPEG 750 azide led to the generation of ABA type triblock copolymers where the middle block is a periodically grafted amphiphilic block and the two linear end blocks are hydrophilic in nature. Furthermore, such propargyl-terminated polyalkylene itaconates were used as macromonomers to prepare multiblock copolymers. The telechelic polymers were first

treated with PEG 600 diazide, resulting in the formation of alternating multiblock copolymers; these multiblock copolymers were further reacted with thioglycerol to generate amphiphilic multiblock copolymers where one of the blocks is a periodically functionalized amphiphilc block, as depicted in Scheme 10. In both these amphiphilic block copolymer systems, a key feature is that the periodically functionalized amphiphilic block folds into a zigzag form, as evident from the presence of a nearly invariant melting peak corresponding to the crystallization of the alkylene segment.



Scheme 10. *Preparation of multiblock copolymers utilizing propargyl-terminated polyalkylene itaconates as a macromonomer.*

In summary, the thesis has demonstrated the design and synthesis of a series of novel amphiphilic copolymers using a bio-sourced monomer, wherein the driving theme is the immiscibility driven self-segregation that leads to the folding of the chain; these have been thoroughly examined using DSC, SAXS, WAXS, variable temperature FT-IR and AFM measurements.

References

(1) Berda, E. B.; Lande, R. E.; Wagener, K. B. *Macromolecules* **2007**, *40*, 8547.
(2) Roy, R. K.; Gowd, E. B.; Ramakrishnan, S. *Macromolecules* **2012**, *45*, 3063.
(3) Mandal, J.; Krishna Prasad, S.; Rao, D. S. S.; Ramakrishnan, S. *Journal of the American Chemical Society* **2014**, *136*, 2538.
(4) Mandal, J.; Ramakrishnan, S. *Langmuir* **2015**, *31*, 6035.